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L11           0 FILE MEDLINE
L12          46 FILE CAPLUS
L13           0 FILE BIOSIS
L14           0 FILE EMBASE

TOTAL FOR ALL FILES
L15          46 L10 AND L8

=> s (l4 or l5 or l6) and l15

L16           0 FILE MEDLINE
L17           1 FILE CAPLUS
L18           0 FILE BIOSIS
L19           0 FILE EMBASE

TOTAL FOR ALL FILES
L20           1 (L4 OR L5 OR L6) AND L15

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L20  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2001 ACS
2000:241135  Document No. 132:279106  Non-peptide GnRH agents, methods and
     intermediates for their preparation.  Anderson, Mark Brian; Vazir, Haresh
     N.; Luthin, David Robert; Paderes, Genevieve Deguzman; Pathak, Ved P.;
     Christie, Lance Christopher; Hong, Yufeng; Tompkins, Eileen Valenzuela;
     Li, Haitao; Faust, James (Agouron Pharmaceuticals, Inc., USA; et al.).
     PCT Int. Appl. WO 2000020358 A2 20000413, 444 pp.  DESIGNATED STATES: W:
     AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK,
     EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP,
     KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL,
     PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN,
     YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF,
     CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML,
     MR, NE, NL, PT, SE, SN, TD, TG.  (English).  CODEN: PIXXD2.  APPLICATION:
     WO 1999-US18790 19990820.  PRIORITY: US 1998-97520 19980820.
GI
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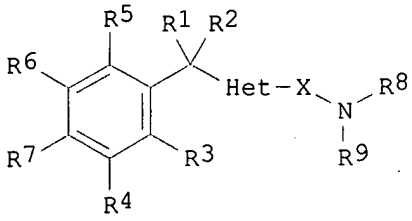

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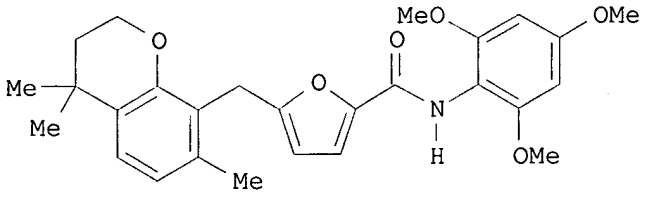


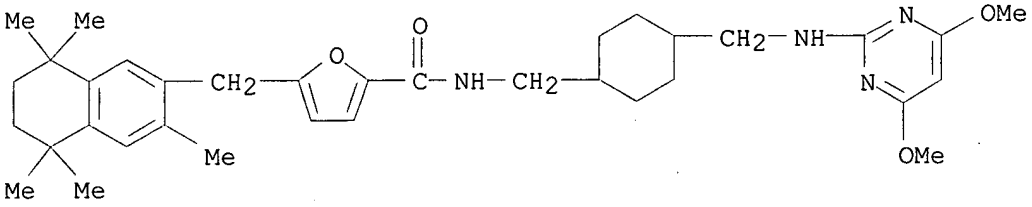
II

AB Non-peptide GnRH agents capable of inhibiting the effect of gonadotropin-releasing hormone are described. The compds. and their pharmaceutically acceptable salts, multimers, prodrugs, and active metabolites are suitable for treating mammalian reproductive disorders and steroid hormone-dependent tumors as well as for regulating fertility, where suppression of gonadotropin release is indicated. The compds. include those of formula I [X = C:O, C:S, S:O, or SO2; Het = 5-membered NOS-heterocycle; R1, R2 = H, alkyl; R3-R7 = H, halo, (un)substituted alkyl, aryl, heteroaryl, CH2OR, OR, CO2R; R = alkyl, aryl, etc.; adjacent rings positions such as R6R7 may form (un)substituted 5- or 6-membered ring with up to 4 heteroatoms; R8 = lipophilic moiety such as alkyl, aryl, CH2OR, OR, etc.; R9 = H, (un)substituted alkyl]. Methods and intermediates for synthesizing the compds. are also described. For instance, 4,4,7-trimethylchroman (prepn. given) was alkylated in the 6- and 8-positions using Et 5-(chloromethyl)-2-furoate (46% total yield), and the resulting esters were hydrolyzed to a mixt. of acids. This unsepd. mixt. was treated with SOCl2 and amidated with 2,4,6-trimethoxyphenylamine-HCl to give the invention compd. II and its chroman-6-position isomer, which were sepd. by HPLC. Several compds. exhibited high affinity (<100 nM) at human GnRH receptors. The compds. antagonized GnRH-stimulated inositol phosphate accumulation in cells with recombinant human GnRH receptors, and an example compd. reduced plasma LH levels in castrated male rats. Various biol. data for several hundred compds. are given.

IT **263848-23-3P 263851-39-4P 263857-23-4P 263857-27-8P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP

(Preparation); USES (Uses)
(target compd.; prepn. of non-peptide GnRH agents for regulating gonadotropin secretion)

RN 263848-23-3 CAPLUS
CN 2-Furancarboxamide, N-[[4-[[(4,6-dimethoxy-2-pyrimidinyl)amino]methyl]cyclohexyl]methyl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)



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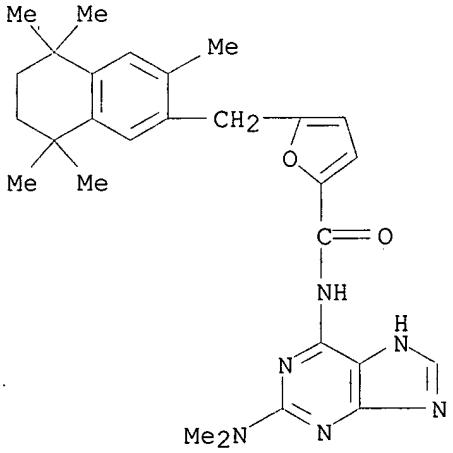
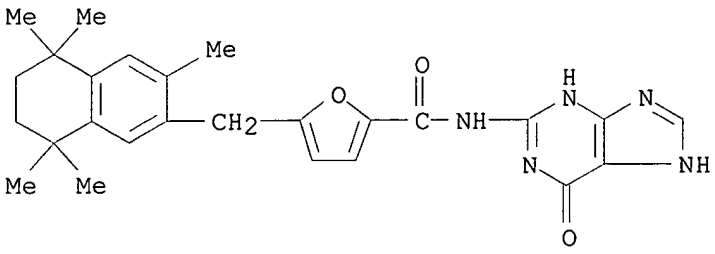
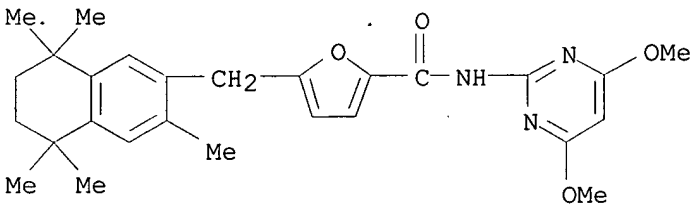
CN 2-Furancarboxamide, N-[2-(dimethylamino)-1H-purin-6-yl]-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)



RN 263857-23-4 CAPLUS
CN 2-Furancarboxamide, N-(6,7-dihydro-6-oxo-1H-purin-2-yl)-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)



RN 263857-27-8 CAPLUS
CN 2-Furancarboxamide,
N-(4,6-dimethoxy-2-pyrimidinyl)-5-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)methyl]- (9CI) (CA INDEX NAME)



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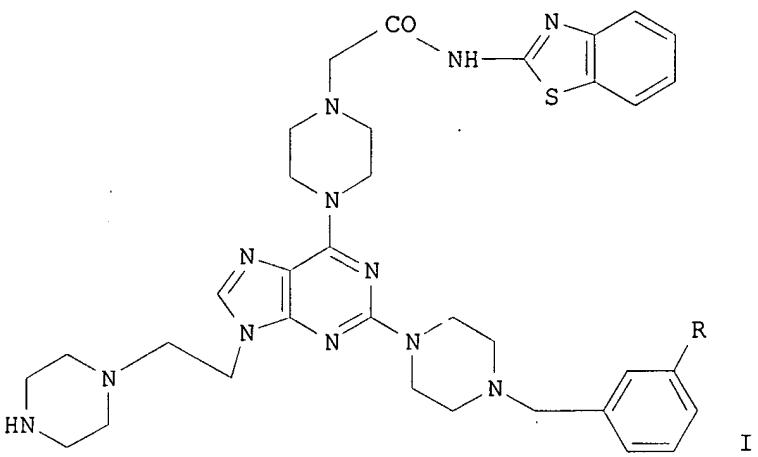
L21 0 FILE MEDLINE
L22 15 FILE CAPLUS
L23 0 FILE BIOSIS
L24 0 FILE EMBASE

TOTAL FOR ALL FILES
L25 15 COOK P?/AU AND (L4 OR L5 OR L6 OR L8 OR L10)

=> d 1-15 cbib abs

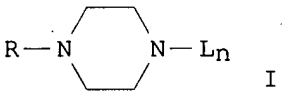
L25 ANSWER 1 OF 15 CAPLUS COPYRIGHT 2001 ACS
1999:448734 Document No. 131:271753 Purine based combinatorial chemistry: solution phase simultaneous addition of functionalities. Iterative deconvolution by orthogonal protection to a single compound with potent antibacterial activity. Fraser, A. S.; Kawasaki, A. M.; **Cook, P. D.** (Department of Medicinal Chemistry, Isis Pharmaceuticals, Inc., Carlsbad, CA, 92008, USA). Nucleosides Nucleotides, 18(4 & 5), 1087-1089 (English) 1999. CODEN: NUNUD5. ISSN: 0732-8311. Publisher: Marcel Dekker, Inc..
GI



I

AB Symposium where the authors describe the synthesis and antibacterial activity of orthogonally piperazine-protected purines (I) (R = Cl, CF3) via soln. phase simultaneous addn. of functionalities.

L25 ANSWER 2 OF 15 CAPLUS COPYRIGHT 2001 ACS
1999:42619 Document No. 130:110283 Nucleobase heterocyclic combinatorialization. **Cook, Phillip Dan**; An, Haoyun; Guinosso, Charles J.; Fraser, Allister S.; Kawasaki, Andrew M. (Isis Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 9900669 A1 19990107, 129 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US13666 19980630. PRIORITY: US 1997-884873 19970630.
GI



I

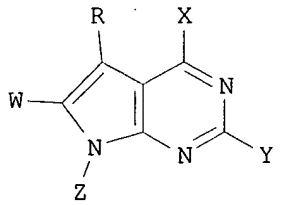
AB Mixts. of title compds. [I; Ln = alkyl, alkynyl, carbocycloalkyl, aryl, heteroaryl, etc.; R = C6H5, 2-pyrimidyl, 2-purinyl, etc.] are prepd., preferably in soln. phase from the reaction of a purine or pyrimidine heterocyclic scaffold with a set of related chem. substituents, optionally through employment of a tether moiety, having antibacterial and other biol. activities per se and are articles of commerce. Thus, the title compd. I (Ln = 2-(4-BOC-1-piperazinyl-6-aminopyrimidyl); R = BOC) was prepd. from 2,4,6-trichloropyrimidine and I (R = H; Ln = BOC).

L25 ANSWER 3 OF 15 CAPLUS COPYRIGHT 2001 ACS
1998:719165 Document No. 129:331055 Improved preparation of oligomeric peptide nucleic acid (PNA) combinatorial libraries. **Cook, Phillip Dan**; Kiely, John; Sprankle, Kelly (Isis Pharmaceuticals Inc, USA). U.S. US 5831014 A 19981103, 33 pp. Cont.-in-part of U.S. 5,539,083. (English). CODEN: USXXAM. APPLICATION: US 1996-693144 19960813. PRIORITY: US 1994-200742 19940223; WO 1995-US2182 19950222.
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB New sub-monomer synthetic methods for the prepn. of peptide nucleic acid oligomeric structures are disclosed that provide for the synthesis of both predefined sequence peptide nucleic acid oligomers as well as random sequence peptide nucleic acid oligomers. Further these methods also provide for the incorporation of peptide nucleic acid units or strings of such units with amino acids or strings of amino acids in chimeric peptide nucleic acid-amino acid compds. Further disclosed are methods of making random libraries of peptide nucleic acids using the fully preformed monomers. Thus, a combinatorial library of chimeric peptide nucleic acid oligomers was prepd. using protected 2-oxomorphilone building blocks I-IV, which involved coupling of IV to a MBHA resin, Mitsunobu reaction of the resulting resin-bound hydroxy adduct with (Boc)2NH using Ph3P and di-Et azodicarboxylate, random coupling of the resulting resin-bound peptide nucleic acid monomer with a mixt. of I, II, III, and IV followed by Mitsunobu reaction for converting the terminal hydroxy group to the terminal amine moieties, repeating the latter procedure for extension of backbone and addn. of further nucleoside bases to complete the oligomer of the desired length, addn. of a peptide to the peptide nucleic acid unit using std. solid phase Merrifield peptide synthesis, and cleavage of peptide nucleic acid oligomers from the resin.

L25 ANSWER 4 OF 15 CAPLUS COPYRIGHT 2001 ACS
1997:701486 Document No. 127:319212 Preparation of antisense substituted purine-containing crosslinking oligodeoxyribonucleotides. **Cook, Phillip Dan**; Manoharan, Muthiah; Ramasamy, Kanda S. (ISIS Pharmaceuticals, Inc., USA). U.S. US 5681941 A 19971028, 57 pp. Cont.-in-part of U.S. Ser. No. 463358, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1994-189792 19940201. PRIORITY: US 1990-463358 19900111; US 1990-566977 19900813.
GI



I

AB Purine-based compds. I (R = alkyl; X = H, OH, amine, alkoxy; Y = halogen, NH2, H, alkyl; W = H, alkyl, alklamine; Z = H, nitrogen protecting group, sugar) were prepd. for incorporation into oligodeoxyribonucleotides. The compds. of the invention, when incorporated into oligodeoxyribonucleotides are esp. useful as antisense agents that are capable of specific hybridization with a nucleotide sequence of an RNA. The compds. of the invention may also be used for crosslinking oligonucleotides. Oligonucleotides are used for a variety of therapeutic and diagnostic purposes, such as treating diseases, regulating gene expression in exptl. systems, assaying for RNA and for RNA products through the employment of antisense interactions with such RNA, diagnosing diseases, modulating the prodn. of proteins, and cleaving RNA in site specific fashions. The compds. of the invention include novel heterocyclic bases, nucleosides, and nucleotides. When incorporated into oligonucleotides, the compds. of the invention can be useful for modulating the activity of RNA.

L25 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2001 ACS

1996:661377 Document No. 126:31563 Oligonucleotides bearing cationic N2-(3-aminopropyl)deoxyguanosine. Synthesis, enhanced binding properties and conjugation chemistry. Manoharan, Muthiah; Ramasamy, Kanda S.; Mohan, Venkatraman; **Cook, P. Dan** (Dep. Med. Chem., Isis Pharm., Karlovy vary, CA, 92008, USA). Tetrahedron Lett., 37(43), 7675-7678 (English) 1996. CODEN: TELEAY. ISSN: 0040-4039. Publisher: Elsevier.

AB A phosphoramidite with an aminopropyl group placed at the N2- position of 2'-deoxyguanosine has been synthesized and incorporated into oligodeoxyribonucleotides. This modification shows enhanced binding properties against both DNA and RNA targets and is useful for conjugating other functionalities.

L25 ANSWER 6 OF 15 CAPLUS COPYRIGHT 2001 ACS

1996:494754 Document No. 125:222358 Backbone modified oligonucleotide analogs and solid phase synthesis of them. **Cook, Phillip D.**; Sanghvi, Yogesh S.; Morvan, Francois (Isis Pharmaceuticals, Inc., USA). U.S. US 5541307 A 19960730, 17 pp. Cont.-in-part of U.S. 5,386,023. (English). CODEN: USXXAM. APPLICATION: US 1993-174379 19931228. PRIORITY: US 1990-558663 19900727; US 1990-566836 19900813; US 1991-703619 19910521; US 1992-903160 19920624; US 1993-40903 19930331.

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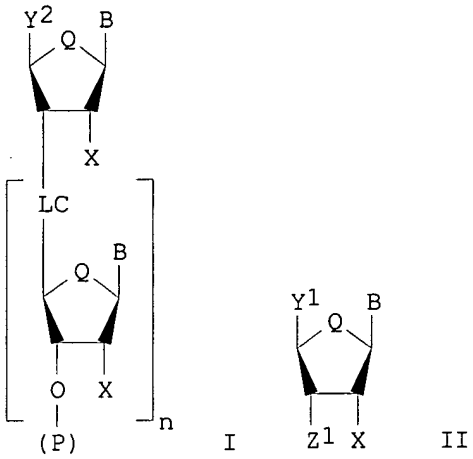


AB Compds. and methods for prepg. oligonucleotide analogs are provided. In preferred embodiments, the methods involve solid-phase coupling of synthons bearing either 3'-electrophilic groups and 5'-nucleophilic groups or 5'-electrophilic groups and 3'-nucleophilic groups to form neutral, achiral oligomers. This process for forming covalent linkages comprises the steps of: (a) providing a support-bound synthon having structure I and

(b) contacting said support-bound synthon with a soln.-phase synthon having structure II, said contacting being for a time and under reaction conditions effective to form a covalent linkage having structure CHN:RACH2, CH2CH:NRA, CH2RAN:CH, or RAN:CHCH2; wherein: Z1 and Y2 are selected such that (i) Z1 is C(O)H and Y2 is CH2RANH2; or (ii) Z1 is CH2RANH2 and Y2 is C(O)H; or (iii) Z1 is CH2C(O)H and Y2 is RANH2 ; or (iv) Z1 is RANH2 and Y2 is CH2 C(O)H; each RA is, independently, O or NR2 ; Y1 is OH, ORHP, CH2OH, or CH2ORHP where RHP is a hydroxyl protecting group; (P) is a solid support; each LC is, independently, a covalent linkage having the structure CH:NRACH2, CH2CH:NRA, CH2RAN:CH, RAN:CHCH2, OP(O)2OCH2, or OP(S)(O)OCH2; n is 0-200; each R2 is, independently, H; alkyl or substituted alkyl having 1 to about 10 carbon atoms; alkenyl or substituted alkenyl having 2 to about 10 carbon atoms; alkynyl or substituted alkynyl having 2 to about 10 carbon atoms; alkaryl, substituted alkaryl, aralkyl, or substituted aralkyl having 7 to about 14 carbon atoms; each B is, independently, a nucleosidic base; each Q is, independently, O or S; and each X is, independently, H, OH, alkyl or substituted alkyl having 1 to about 10 carbon atoms, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, or N-alkyl. Thus, e.g., 5'-O-phthalimidothymidine was loaded onto succinyl-CPG whose free amino groups were capped [HO2C(CH2)2CONMe-CPG-NMe2] to provide 5'-O-phthalimido-3'-O-(succinyl-CPG-NMe2)thymidine; deprotection to the 5'-O-amino was followed by 10 cycles of coupling/deprotection with 5'-O-phthalimido-3'-formyl-3'-deoxythymidine and a final coupling with 5'-tert-butyldiphenylsilyl-3'-formyl-3'-deoxythymidine to provide a bound oxime-linked oligonucleoside; redn. of the latter with NaCNBH3 provided the bound aminohydroxyl-linked oligonucleoside which upon methylation with formaldehyde/NaCNBH3 provided the bound oligomer with 3'-de(oxyphosphinico)-3'-[methylene(methylimino)] 3'-CH2-NMe-O-5' backbone; oligomer was cleaved from the solid support with

30% NH3, deprotected with TBAF, and purified to provide T12 with 3'-de(oxyphosphinico)-3'-[methylene(methylimino)] backbone.

L25 ANSWER 7 OF 15 CAPLUS COPYRIGHT 2001 ACS
1995:994345 Document No. 124:146851 Preparation of oligomeric peptide nucleic acid (PNA) combinatorial libraries and improved methods of synthesis. **Cook, Philip Dan**; Kiely, John; Sprankle, Kelly (Isis Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 9523163 A1 19950831, 103 pp. DESIGNATED STATES: W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1995-US2182 19950222. PRIORITY: US 1994-200742 19940223.

AB New sub-monomer synthetic methods for the prepn. of peptide nucleic acid oligomeric structures, useful as inhibitors of enzymes such as phospholipase A2 and for the treatment of inflammatory diseases including atopic dermatitis and inflammatory bowel disease (no data), are disclosed, that provide for the synthesis of both predefined sequence peptide nucleic acid oligomers as well as random sequence peptide nucleic acid oligomers. Further these methods also provide for the incorporation of peptide nucleic acid units or strings of such units with amino acids or strings of amino acids in chimeric peptide nucleic acid-amino acid compds. Further disclosed are methods of making random libraries of peptide nucleic acids using the fully preformed monomers. Thus, a combinatorial library of chimeric peptide nucleic acid oligomers was prepd. using 1-[(N2-benzyloxycarbonyl-N6-benzyloxy-2-aminopurin-9-yl)acetyl]-2-oxomorpholine (I), 1-[(N6-benzyloxycarbonyladenin-9-yl)acetyl]-2-oxomorpholine (II), 1-[(N4-benzyloxycarbonylcytosin-1-yl)acetyl]-2-oxomorpholine (III), and 1-(thymin-1-ylacetyl)-2-oxomorpholine (IV), which involved coupling of IV to a MBHA resin, Mitsunobu reaction of the resulting N-(thymin-1-ylacetyl)-N-(2-hydroxyethyl)glycine-MBHA resin with (Boc)2NH using Ph3P and di-Et azodicarboxylate, random coupling of the resulting N-(thymin-1-ylacetyl)-N-(2-aminoethyl)glycine-MBHA resin with a mixt. of I, II, III, and IV followed by Mitsunobu reaction for converting the terminal hydroxy group to the terminal amine moieties, repeating the latter procedure for extension of backbone and addn. of further nucleoside bases to complete the oligomer of the desired length, addn. of a peptide to the peptide nucleic acid unit using std. solid phase Merrifield peptide synthesis, and cleavage of peptide nucleic acid oligomers from the resin.

L25 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2001 ACS
1995:960186 Document No. 124:202953 N-2 Substituted purines and their use in oligonucleotides and antisense agents. **Cook, Phillip Dan**; Ramasamy, Kanda S.; Manoharan, Muthiah (Isis Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 9514707 A1 19950601, 94 pp. DESIGNATED STATES: W: JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US13622 19941129.

PRIORITY: US 1993-159088 19931129.

GI

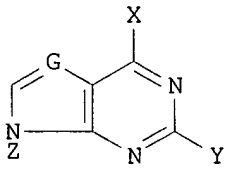
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention presents novel purine-based compds. I [G = CH, N; X = NH2, OH; Y = RQ, NHRQ; R = H, C2-20 hydrocarbondiyl; Q = .gtoreq. 1 reactive or non-reactive functionality; Z = H, N-protecting group, sugar moiety] for inclusion in oligonucleotides. I, when incorporated into oligonucleotides, are esp. useful as "antisense" agents capable of specific hybridization with an RNA nucleotide sequence. Uses (no data) include treating diseases, regulating gene expression in exptl. systems, assaying for RNA and for RNA products, diagnosing diseases, modulating prodn. of proteins, and site-specific cleavage of RNA. I include novel heterocyclic bases, nucleosides, and nucleotides. For example, reaction of 2-chloro-9-(2'-deoxy-.beta.-D-erythro-pentofuranosyl)inosine [prepn. given] reacted with 1-(3-aminopropyl)imidazole to give 67% guanosine intermediate II, which underwent a sequence of N2,3',5'-triacylation with isobutyryl chloride (77%), 6-O-etherification with p-O2NC6H4CH2CH2OH by Mitsunobu reaction (96%), di-O-deacylation (81%), 5'-O-protection with 4,4'-dimethoxytrityl chloride (80%), and reaction with i-Pr2NPClOCH2CH2CN (65%), to give title compd. III (i.e. G'). When incorporated into the modified oligonucleotide CGACTATGCAAG'G'G'C, the G' residue increased Tm of its DNA hybrid by 2.8.degree./mod vs. wild. Prepns. of several addnl. I and Tm results for 18 modified oligonucleotide sequences are given.

L25 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2001 ACS

1995:951494 Document No. 124:176818 N2-Substituted purines for inclusion into oligonucleotide antisense agents. **Cook, P. Dan**; Ramasamy, Kanda S.; Manoharan, Muthiah (Isis Pharmaceuticals, Inc., USA). U.S. US 5459255 A 19951017, 26 pp. Cont.-in-part of U.S. Ser. No. 463, 358, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1993-159088 19931129. PRIORITY: US 1990-463358 19900111; US 1990-566977 19900813; US 1992-854634 19920701.

GI



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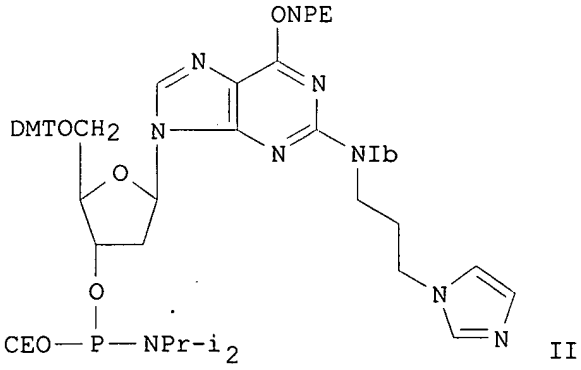


II

AB This invention presents novel purine-based compds. I wherein G is CH or N;
X is NH2 or OH; Y is RQ or NHRQ, wherein said R is a hydrocarbyl group having from 2 to about 20 carbon atoms; and Q is H, NH2, polyalkylamino, hydrazines, hydroxylamines, imidazoles, imidazole amides, alkylimidazoles, tetrazole, triazole, or alkoxy groups; and Z is ribose or deoxyribose, for inclusion into oligonucleotides. The compds. of the invention, when incorporated into oligonucleotides are esp. useful as agents that are capable of specific hybridization with a nucleotide sequence of an RNA. Oligonucleotides are used for a variety of purposes, such as regulating gene expression in exptl. systems, assaying for RNA and for RNA products through the employment of interactions with such RNA, diagnosing diseases, modulating the prodn. of proteins, and cleaving RNA in site specific fashions. The compds. of the invention include novel heterocyclic bases, nucleosides, and nucleotides. When incorporated into oligonucleotides, the compds. of the invention can be useful for modulating the activity of RNA. Thus, e.g., treatment of 5'-O-(4,4'-dimethoxytrityl)-6-O-[2-(4-nitrophenyl)ethyl]-N2-isobutyryl-N2-[3-(imidazol-1-yl)propyl]-2'-deoxy-.beta.-D-erythro-pentofuranosylguanine (prepn. given) with (.beta.-cyanoethoxy)chloro(N,N-diisopropylamino)phosphine afforded N2-imidazolylpropyl deoxyguanosine amidite synthon II which was incorporated into oligonucleotide sequences via automated DNA synthesis protocol. A 21-mer oligonucleotide [5'd-(GCCGAGGTCCATGTCGTACGC)] was modified with one, three or seven N2-[3-(1H-imidazol-1-yl)propyl]dGs or one or three N2-[3-(1H-imidazol-1-yl)propyl]-2-NH2-dAs and hybridized to complementary DNA or RNA. Compared to unmodified DNA, the av. change Tm/mod was +2.0 and +0.3 for dG modified oligonucleotides hybridized with DNA and RNA, resp.; the av. change Tm/mod was +2.7 and +0.6 for dA modified oligonucleotides hybridized with DNA and RNA, resp.

L25 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2001 ACS
1995:896318 Document No. 124:23293 Substituted purines, oligonucleotides containing them for RNase H cleavage of RNA, and crosslinked nucleic acids. **Cook, Phillip Dan**; Manoharan, Muthiah; Ramasamy, Kanda S. (ISIS Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 9521184 A1 19950810, 175 pp. DESIGNATED STATES: W: JP, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1995-US1361 19950201. PRIORITY: US 1994-189792 19940201.
GI For diagram(s), see printed CA Issue.
AB This invention is directed to novel purine analogs I (G=H,A; A=C1-20-hydrocarbyl; X=halogen, NH2, OH, NHRQ, ORQ; R=H,A; Q=reactive/nonreactive functionality; Y=halogen, NH2, RQ, NHRQ; W=H, RQ, NHRQ; Z=H, sugar moiety, N protecting group) which may be incorporated into oligonucleotides. The compds. of the invention, when incorporated into oligonucleotides, are esp. useful as "antisense" agents -- agents that are capable of specific hybridization with a nucleotide sequence of an RNA. The compds. of the invention may also be used for crosslinking oligonucleotides. Many purine analog phosphoramidites were prepd. and some were used to prep. oligonucleotides. Oligonucleotides complementary to human ICAM-1 nucleic acid and contg. N2-propylaminoguanine were reacted with such compds. as fluorescein isothiocyanate and bromoacetic acid

N-hydroxysuccinimide ester.

L25 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2001 ACS
1995:605386 Document No. 123:83946 Preparation of acyclic nucleoside analogs
and antisense oligonucleotide sequences containing them. **Cook, Philip D.**; Delecki, Daniel J.; Guinosso, Charles (Sterling Winthrop Inc., USA). PCT Int. Appl. WO 9422864 A1 19941013, 37 pp. DESIGNATED STATES: W: AU, BR, CA, CZ, FI, HU, JP, KR, NO, NZ, RU, SK, UA; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US2995 19940321. PRIORITY: US 1993-40326 19930330.
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Acyclic nucleoside analogs (I; R1 = H or a blocking group that is compatible with oligonucleotide synthesis; R2 = H, Me; R3 = H, P(R4)OR5; wherein R4 = Cl, 4-nitroimidazole, imidazole, tetrazole, triazole, or di(lower-alkyl)amino; R5 = Me, 2-cyanoethyl, or 2,2,2-trichloroethyl; n = 0 - 2; X = O, S, or NR6; wherein R6 = H, lower alkyl; Q is chosen from the group consisting of Q1 and Q2; wherein R7 = lower alkyl; R8 = H, benzoyl, anisoyl, or lower alkylcarbonyl) and its pharmaceutically acceptable addn. salts are prepd. Modified oligonucleotides contg. the nucleoside analogs of formula I are stable to nuclease degrdn. and are useful in inhibiting gene expression, in sequencing, and in mutagenesis. Thus, an oligomer 5'-CCTTCTCA*GTCGGA*C-3' (II; A* = acyclic nucleoside residue Q2) was synthesized by using std. procedures on a DNA synthesizer (Applied Biosystems model 380B) and an acyclic nucleoside phosphoramidite (III; DMT = dimethoxytrityl) (prepn. given). Using rabbit reticulocyte lysate, II at 30 .mu.M inhibited cell free-translation of rabbit .alpha.-globin mRNA by 74.+-.10% in the absence of RNase H and 84.+-.5% in the presence of RNase H.

L25 ANSWER 12 OF 15 CAPLUS COPYRIGHT 2001 ACS
1995:315537 Document No. 122:106399 Preparation of novel 2'-O-alkylnucleosides and phosphoramidites processes for the preparation and uses thereof for the synthesis of oligonucleotides. McGee, Daniel Peter Claude; **Cook, Phillip Dan**; Guinosso, Charles John (ISIS Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 9402501 A1 19940203, 85 pp. DESIGNATED STATES: W: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, VN; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1993-US6807 19930720. PRIORITY: US 1992-918362 19920723; US 1992-967267 19921027; US 1992-968849 19921030.
GI

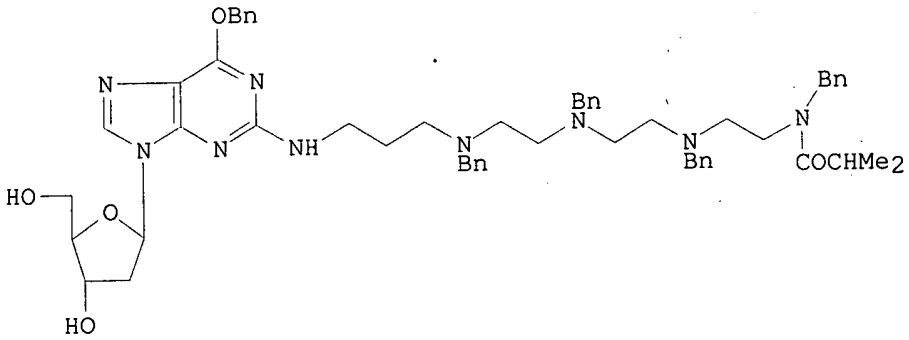
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Novel 2'-O-alkylguanosine compds. [I; X = R1-(R2)n; R1 = C3-20 alkyl, C4-20 alkenyl, C2-20 alkynyl; R2 = halo, OH, SH, keto, CO2H, NO2, nitroso, cyano, CF3, CF3O, alkoxy, alkylthio, alkylamino, NH2, phthalimido, imidazolyl, N3, hydrazino, HONH, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocyclyl, carbocyclyl, intercalator, reporter mol., conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic or pharmacokinetic properties of oligonucleotides; n = 0-6] and their derivs.. [II; X = R1-(R2)n; R1 = C3-20 alkyl; R2 = NH2, imidazolyl, phthalimido; Y = HO-blocking group; Q1, Q2 = H, guanosine-blocking group; n = 0-6] and 2'-O-alkyl-2,6-diaminopurine compds. (III; X = same as described in I) are prepd. 2'-O-alkylguanosine I is prepd. by treating 2,6-diaminopurine riboside with a base and R-L (R = alkyl; L = a leaving group) to form 2'-O-alkyl and 3'-O-alkyl-2,6-diaminopurine and deaminating said 2'-O-alkyl-2,6-diaminopurine in the presence of adenosine deaminase. Processes for prepg. 2'-O-alkylated guanosine, uridine, cytidine, and 2,6-diaminopurine 3'-O-phosphoramidites are also provided. 2'-O-alkylnucleoside 3'-O-phosphoramidites are used for prepg. antisense oligonucleotides by the phosphoramidite method. Thus, a mixt. of 49 g guanosine hydrate, toluene 200, hexamethyldisilazane 160, and CF3SO3H 3.7 mL was heated in a stainless steel Parr bomb at 170.degree. for 5 days to give 89% III (X = H) which was treated with NaH in DMF for 10 min and alkylated by iodopropane in DMF at room temp. overnight to give, after silica gel chromatog., 5.3 g 2'-O-Pr isomer III (X = Pr) and 4 g of a mixt. of 2'- and 3'-O-Pr isomers. The latter mixt. (4.6 g) and 200 mg adenosine deaminase were stirred at room temp. overnight in 0.1 M tris buffer (pH 7.4), DMSO, and 0.1 M Na phosphate buffer followed by adding a further aliquot of 140 mg adenosine deaminase in 0.1 M phosphate buffer and DMSO and stirring for addnl. 24 h to give 2.6 g I (X = Pr). The latter compd. (3.6 g) was silylated by Me3SiCl in pyridine and then acylated by isobutyryl chloride to give 2.5 g N2-isobutyryl-2'-O-propylguanosine which was tritylated by dimethoxytrityl chloride in pyridine at room temp. to give 4.1 g 5'-O-trityl deriv. This (4.1 g) was then condensed with bis(N,N'-diisopropylamino)-2-cyanoethylphosphite in the presence of N,N-diisopropylammonium tetrazolide in CH2Cl2 to give 5.2 g a phosphoramidite (IV).

L25 ANSWER 13 OF 15 CAPLUS COPYRIGHT 2001 ACS
1994:409916 Document No. 121:9916 Remarkable enhancement of binding affinity of heterocycle-modified DNA to DNA and RNA. Synthesis, characterization and biophysical evaluation of N2-imidazolylpropylguanine and N2-imidazolylpropyl-2-aminoadenine modified oligonucleotides. Ramasamy, Kanda S.; Zounes, Maryann; Gonzalez, Carolyn; Freier, Susan M.; Lesnik, Elena A.; Cummins Lendell L.; Griffey, Richard H.; Monia, Brett P.; **Cook, P. Dan** (ISIS Pharm., Carlsbad, CA, 92008, USA). Tetrahedron Lett., 35(2), 215-18 (English) 1994. CODEN: TELEAY. ISSN: 0040-4039.
AB Oligonucleotides contg. novel N2-imidazolylpropylguanine and N2-imidazolylpropyl-2-aminoadenine moieties were synthesized and studied for their hybridization and biophys. properties. Interestingly, these

heterocycle modified oligonucleotides showed a remarkable enhancement of heteroduplex binding affinity when hybridized to complementary DNA.

L25 ANSWER 14 OF 15 CAPLUS COPYRIGHT 2001 ACS
1994:299184 Document No. 120:299184 Synthesis of 2'-deoxyguanosine containing a N2-polyamine. Ramasamy, Kanda S.; Bakir, Farid; Baker, Brenda; **Cook, P. Dan** (ISIS Pharm., Inc., Carlsbad, CA, 92008, USA). J. Heterocycl. Chem., 30(5), 1373-7 (English) 1993. CODEN: JHTCAD.
ISSN: 0022-152X.
GI



I

AB The synthesis of benzylated tetraazatridecyldeoxyguanosine I was accomplished by a key nucleophilic reaction of the novel unsym. polyamine H2N(CH2)3NBn(CH2)2NBn(CH2)2NBn(CH2)2NHBn with 3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)-2-chloro-2'-deoxyinosine.

L25 ANSWER 15 OF 15 CAPLUS COPYRIGHT 2001 ACS
1991:672717 Document No. 115:272717 Nuclease-resistant modified oligonucleotide for detecting and modulating RNA activity and gene expression. **Cook, Philip Dan**; Ecker, David J.; Guinosso, Charles John; Acevedo, Oscar Leobardo; Kawasaki, Andrew Mamoto; Ramasamy, Kandasamy (Isis Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 9110671 A1
19910725, 194 pp. DESIGNATED STATES: W: AU, BR, CA, FI, HU, JP, KR, NO, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1991-US243 19910111. PRIORITY: US 1990-463358 19900111; US 1990-566977 19900813.
AB Oligonucleotide analogs contg. modified sugars are prepd. for use in antisense oligonucleotide diagnostics and therapeutics. Protected 2'-o-nonyladenosine phosphoramidate was prepd. and incorporated by solid phase synthesis into 15-mers complementary to a portion of the papillomavirus genome. The Tm of the unmodified 15-mer and the Tm's of the 15-mers contg. 1 of 3 adenosine analogs were comparable but the nuclease resistance was increased approx. 5- and 64-fold, resp.

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